# Use of N-acetyl-D-glucosamine in treatment of local lesions or systematic symptoms caused by infections of virus or bacteria

**IEC040019PCT**

## Technical field

The present invention relates to the use of N-acetyl-D-glucosamine or pharmaceutically acceptable salts thereof in the treatment of local lesions and/or systematic symptoms caused by infections of virus and/or bacteria, and the use of N-acetyl-D-glucosamine or pharmaceutically acceptable salts thereof in the manufacture of a medicament for the treatment of local lesions and/or systematic symptoms caused by infections of virus and/or bacteria.

## Background Art

The systematic toxic symptoms caused by infections of virus and/or bacteria include systematic toxic symptoms caused by endotoxemia and local ectotoxic lesions, such as fever, headache, vertigo, delirium, nausea, emesis, general malaise, etc. At present, there are two main methods for treatment of systematic symptoms caused by infections of bacteria: 1) antibacterial therapy, and 2) supporting therapy.

Viral infections are commonly caused but not limited by Coxsackie virus, ECHO virus, orthomyxovirus, paramyxovirus, adenovirus, coronaviruses, reovirus, respiratory syncytial virus, rhinovirus, hepatitis A virus, hepatitis B virus, hepatitis C virus, and encephalitis B virus, which result in systematic symptoms such as fever, etc. accompanying by local mucosal lesions. The most usual symptoms are inflammations, including tracheitis, bronchitis, mucous hyperemia, and exhibit cough and asthma. At present, there is no means or drug to effectively control viral infections, except for some supporting therapies.

In the research of "bio-wave" theory, the present inventor has set up a organism wave-growth model. Through deeply researching the molecular mechanism of the organism wave-growth, the inventor puts forward a micro-heterology variation mechanism, wherein the biological wave of organism continuously changes; the change rate depends on the change

extent of outer environments; after the organism is infected by bacteria and viruses, the environments in the organism changes quickly, which promotes the generation of micro-heterology and the non-equilibrium between the organism and environments, and causes local lesions and systematic toxic symptoms. According to molecular biological analysis, these lesions and toxic symptoms relate to the instability even loss of function of proteins, especially various enzymes under changed conditions, especially changed temperature in the presence of microorganism metabolism products. The systematic toxic symptoms mainly appear in nerve system, including headache, delirium, hypersomnia, coma, general malaise, muscular soreness, nausea, emesis, blurred vision, diplopia, respiration disorder (first tachypnea then bradypnea), arrhythmia, urinary and fecal incontinence, even torpidity or loss of reflex, local congestion, edema, blood clot and tissue necrosis.

It is found that N-acetyl-D-glucosamine as a regulating factor of biological wave affects not only the macro fluctuation, but also the stability of vibration of bio-macromolecular substances. This substance can maintain the physiological vibration of bio-macromolecular substances, alleviate and repulse harmful effects in organism, in order to maintain the physiological function of macromolecular substances. In general, said substance can control symptoms, alleviate lesions, promote heal, and eliminate toxic effects.

The inventor surprisingly finds that N-acetyl-D-glucosamine or pharmaceutically acceptable salts in combination with various pharmaceutically acceptable carriers can form a liquid dose form for treatment of local lesions or systematic toxic symptoms caused by infections of virus or bacteria.

**Contents of the invention**

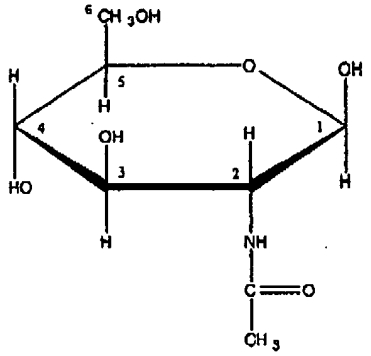
One object of the present invention is to provide a use of N-acetyl-D-glucosamine or pharmaceutically acceptable salts thereof in the treatment and control of local lesions and systematic symptoms caused by infections of virus or bacteria.

Another object of the present invention is to provide a use of N-acetyl-D-glucosamine or pharmaceutically acceptable salts thereof in the

manufacture of a medicament for the treatment and control of local lesions and systematic symptoms caused by infections of virus or bacteria.

Another object of the present invention is to provide a method for treating local lesions and systematic symptoms caused by infections of virus or bacteria.

The N-acetyl-D-glucosamine used in the present invention is a compound having a molecular formula of $C_8H_{15}NO_6$ and a structure formula (I).



The examples of pharmaceutical acceptable salts of N-acetyl-D-glucosamine that can be used in the present invention include, but are not limited to: the salts formed with inorganic acids, such as hydrochloride, hydrobromide, borate, phosphate, sulfate, hydrosulfate and hydrophosphate, and the salts formed with organic acids, such as citrate, benzoate, ascorbate, methylsulfate, picrate, fumarate, maleate, malonate, succinate, tartrate, mesylate, and glucose-1-phosphate.

In a pharmaceutical composition of the present invention, the content of N-acetyl-D-glucosamine or pharmaceutically acceptable salts thereof is generally 0.1-10% by weight.

Besides N-acetyl-D-glucosamine or pharmaceutically acceptable salts thereof, said pharmaceutical composition further comprises excipients or carriers well known in the art to form a preparation suitable for intravenous injection, subcutaneous injection, intramuscular injection, intraperitoneal injection, etc.

Said pharmaceutical composition can be administered in a manner of single dose per day or multidoses per day, such as 3-4 doses per day. The

dose of said pharmaceutical composition depends on patient's age, condition, symptom, and administration manner. In general, as to an adult patient having a bodyweight of 75 kg, the dose of said pharmaceutical composition is 1-100000 mg per day, preferably 100-10000 mg per day based on active component, and is administered one to four times daily.

According to a preferable model, N-acetyl-D-glucosamine is administered in a manner of intervenous drop infusion during the therapeutical procedure in order to potentiate power of resistance, to replenish water, and to maintain stability in vivo.

As compared to conventional supporting therapy, N-acetyl-D-glucosamine or pharmaceutically acceptable salts thereof are more effective in reducing local inflammations and alleviating local lesions and systematic toxic symptoms, act quickly and roundly, and facilitate better prognostic results.

Although the inventor does not intend to be restricted by any theory, it is believed that N-acetyl-D-glucosamine or pharmaceutically acceptable salts thereof can stabilize important molecules of organism and maintain the physiological function of bio-macromolecules, thereby avoiding some complications after infections of virus or bacteria and expediting the healing. Thus, N-acetyl-D-glucosamine or pharmaceutically acceptable salts thereof are desired drug for supporting therapy.

**Embodiments for carrying out the invention**

The present invention and beneficial effects thereof are further demonstrated by the following examples, but it shall be understood that these examples are merely to illustrate the present invention, rather than to restrict the scope of the present invention in any aspect.

Example 1. *Promoting wave test of the compound of formula (I)*

1. Experimental materials and method:

1.1 Sample: pure compound of formula (I)

1.2 Experimental materials:

Strain: *Proteus Mirabilis* that meets the following biochemical reaction

characteristics: dynamics (+), urease (+), lactose (-), glucose (+), $H_2S$ (-),phenylalanine deaminase (+).

Culture medium: modified LB culture medium (components: 1% tryptones, 0.5% yeast extract, 1% sodium chloride, 0.1% glucose, 0.002% TTC, and pH = 7.2 to 7.4).

1.3 Experimental method:

Control sample: the *Proteus Mirabilis* were inoculated at the center of LB plate, incubating at 37°C for 9 hours;

Test sample: the compound of formula (I) with a final concentration of 0.5% was added to the LB plate, then the *Proteus Mirabilis* were inoculated by the same method, and cultured at 37°C for 9 hours.

2. Experimental results and evaluation:

The control sample exhibited concentric rings with an interval of 3 hours, which extended outward continually. The test sample showed not only concentric rings with an interval of 3 hours, but also many fine waves on each ring in comparison with the control sample.

The experiment adopts a bio-wave model to research the promoting wave function of the compound of formula (I). The results showed that the compound of formula (I) was not only able to cause bacterial cell to reveal a normal bio-wave characteristic, but also cause the wave reveal finer wave mode. These indicated that the compound of formula (I) has a function of promoting bio-waves. This wave-promoting function may explain the effects of using N-acetyl-D-glucosamine or pharmaceutically acceptable salts thereof for treating and controlling local lesions and systematic symptoms caused by infections of virus or bacteria.

Example 2. *Toxicological test of the compound of formula (I)*

The toxicological test of the compound of formula (I) includes:

1. Acute toxicity test: including tests of oral administration, intravenous

injection administration, and maximum limit amount for administration;

2. Ames test;
3. Micronucleus test of mouse bone marrow cell;
4. Abnormality test of mouse sperm;
5. Aberration test of mouse testis chromosome;
6. Chronic lethal test;
7. Sub-chronic toxicity (feed for 90 days) test;
8. Traditional deformity-inducing test.

The results of these tests showed that in the acute toxicity test of the compound of formula (I), the acute toxicosis reaction had not appeared when the dosage more than 2 g/kg was taken; in the long-period toxicity test, the maximum dosage had reached up to 1 g/kg, and after the treatment and observation for four weeks, there was no intoxication reaction yet; and in the reproduction test, the mice were feed with a routine dosage of 7 mg/kg for 3 generations, it had been proved that the compound of formula (I) had no influence on the pregnancy, birth, nurse and the growth of baby mouse, so that the compound of formula (I) is a substance without toxicity.

Example 3. *Cytological tests of regulating micro-heterology variation*

Conventional incomplete 1640 culture media were used for cell culture, and B16 tumor cells (commercially obtained from the tumor cell library of Shanghai Institute of Cytobiology) were inoculated on said media. After being continuously cultured for more than 48 hours, the micro-heterology variation of cells and the control effects of N-acetyl-D-glucosamine thereon were observed under a condition where metabolic wastes affected the growth environment. After N-acetyl-D-glucosamine having a final concentration of 1 g/100ml was added to the culture media, the cell number stably increased with the culture time during the cell growth procedure. The control cells cultured without N-acetyl-D-glucosamine could not proliferate on the same culture media under same conditions. These tests indicated that in the presence of the compound of formula (1), cells could regulate the cell micro-heterology variation in order

to adapt to the ever-changing environment, so that cells could proliferate continuously.

Example 4. *Animal tests that N-acetyl-D-glucosamine regulates micro-heterology variation*

B16 tumor cells were inoculated on superior parts of hind legs of 50 rats, and 5% aqueous solution of the compound of formula (1) was intraperitoneally injected to the rats for consecutive 7 days, 3 times per day, and 1ml every time. Finally, solid tumor did not appear in 45 rats. In control group without the administration of the compound of formula (1), many proliferative corpuscles appeared in at least 40 among 50 rats within 1-3 days after the tumor cells were inoculated; many immature cells appeared within 3-5 days; and visible solid tumors finally appeared within about 10 days. As compared to the control group, this did not appear in the test group, which indicated that the compound of formula (1) could control the micro-heterology variation.

Example 5. *Animal tests of controlling local lesions and systemic symptoms caused by infection of microorganism*

10 rabbits were used in tests. The rabbits were administered with a culture of Gram-negative bacteria (Pseudomonas aeruginosa, serotype 8, wherein the bacterial number in the culture is about $3 \times 10^{11}$) in a dose of 10 ml per day for consecutive 3 days. The rabbits exhibited serious toxic symptoms, such as fever, increased heart rate, tachypnea, hyperposia, bodyweight drop, and after 5 days, the rabbits exhibited watery stool, increased nasal secretion, systematic emaciation and exhaustion. The rabbits were intravenously administered with N-acetyl-D-glucosamine (10% aqueous solution) a dose of 2 ml every time, 3 times per day, for consecutive 3 days. The rabbits were gradually healed after one week, they began to eat, their symptoms were alleviated, their body temperatures dropped, and their defecation formed. After examination of nasal mucosa and respiratory tract of the rabbits, the inflammations were alleviated, and their secretion products were normal. In the

test group, all 10 rabbits survived, while in the control group, 8/10 rabbits of the control group died within one week, and only 2 rabbits survived.

When N-acetyl-D-glucosamine was replaced with N-acetyl-D-glucosamine hydrochloride in the tests (other conditions were not changed), 7/10 rabbits of test group survived. The test group was significantly different from the control group.